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Note

Synthesis and structure activity relationships in diphenylureas against *Culex quinouefasciatus*

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Substituted diphenylureas **1-23** have been synthesised from isocyanates generated from azides of benzoic acid and 4-chlorobenzoic acid with aniline, and 4-chloro-, 2-trifluoromethyl-, 3-trifluoromethyl, 4-phenoxy-, 2,4-dichloro-, 2,5-dichloro-, 3,4-dichloro-, 3-chloro-4-methoxy-, 3-chloro- 2-methyl-, 3-chloro-4-methyl- and 4-nitro-anilines. All the compounds have been tested for insect growth regulating (IGR) activity against early third instar larvae of *Culex quinquefasciatus,* the human filariasis vector. Compounds **15** and **19** [1-(4-chlorophenyl)-3-(3-trifluoromethylphenyl) urea and 1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)urea] exhibit 100% emergence inhibition at 1 ppm concentration against *Cx quinquefasciatus* larvae. These compounds may play a useful role in mosquito control by maintaining the vector populations at a minimum level.

During the past decade immense excitement has been created by insect growth regulators in the field of insect control. Insect growth regulators have great prospects in combating insect pests due to their unique mode of action by intervening with certain aspects of their physiology during their life cycle with minimal deleterious impact on the nontarget organisms and the environment. Much work has been done in search of compounds exhibiting insect growth regulating activity. As a result compounds belonging to different classes such as diphenyl ethers[1-3], amides[4], carbamates[5,6], benzoyl phenyl ureas[7-12], phenoxy substituted compounds[13] and benzoyl glycinylamides[14] were identified as insect growth regulators. Our previous work on diphenylureas[15] showed some promising results and herein we report the synthesis and structure activity relationships in 23 diphenylureas studied against *Culex quinquefasciatus*, the human lymphatic filariasis vector.

Results and Discussion

Twenty three diphenylureas **1-23** were synthesised from benzoic acid and 4-chlorobenzoic acid with twelve anilines, *viz.* aniline, 4-chloro-, 2-trifluoromethyl-, 3-trifluoromethyl, 4-phenoxy-, 2,4-dichloro-, 2,5-dichloro-, 3,4-dichloro-, 3-chloro-4-methoxy-, 3-chloro-2-methyl-, 3-chloro-4-methyl- and 4-nitro-anilines. The required acid chlorides were prepared by refluxing the respective acids with thionyl chloride. The acid chlorides on treatment with sodium azide afforded the acid azides which on heating underwent Curtius rearrangement to give the respective isocyanates. Reaction of anilines with isocyanates gave the diphenyl ureas.

All the diphenylureas were obtained in very good yield (80-90%) as crystalline solids having high melting points (cf. Table I). Most of them showed limited solubility in benzene as evidenced from the precipitation in the reaction medium itself during the course of the synthesis.

These compounds were tested against the third instar larvae of *Cx. quinquefasciatus* following the WHO procedure[16,17]. The insect growth regulating (IGR) activity expressed in terms of percentage emergence inhibition (%EI) are given in Table I. *Cx. quinquefasciatus* was found to be highly susceptible to compounds **15** and **19** with %EI values of 100 followed by compounds **6** and **10** with 72 and 70 respectively.

The treated larvae and pupae showed various morphological abnormalities. Dead larvae were elongated and attached to the previous moult. Mortality in the larval-pupal intermediate was prominent.

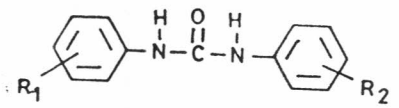
The results show that the activity is enhanced with various substitutions in the aniline moiety in the following order for diphenylureas derived from benzoic acid:

2,4-diCl > 3-Cl,2-CH_3 > 4-Cl >3-CF_3; 2,5-diCl; 3,4-diCl > 4-OPh; H; 4-NO_2 > 2- CF_3 > 3-Cl, 4-OCH_3 > 3-Cl, 4-CH_3.

In the case of diphenylureas derived from 4-chlorobenzoic acid the IGR activity is enhanced with various substitutions in the aniline moiety in the following order:

3-CF_3; 3,4-diCl > 4-NO_2 > 2,4-diCl > 3-Cl, 4-OCH_3 >3-Cl, 4-CH_3 > 2,5-diCl > 3-Cl, 2-CH_3 > 4-Cl; 2-CF_3; 4-OPh.

Table I—Structure, biological activity, physical and spectral data of compounds **1-23**



Compd	R_1	R_2	Yield (%)	m.p. °C	ArH	^{1}HNMR data (δ,ppm) OCH_3	CH_3	-NH-	% EI
1	H	H	80.0	245	6.81-7.79	—	—	8.67	12
2	H	4-Cl	82.5	264	6.93-7.87	—	—	8.94	30
3	H	2-CF_3	85.0	182	6.83-7.92	—	—	9.31	10
4	H	3-CF_3	85.5	220	6.83-7.67	—	—	9.30	24
5	H	4-DPh	90.0	198	6.67-7.71	—	—	8.62	20
6	H	2,4-diCl	81.5	227	6.71-7.71	—	—	9.37	72
7	H	2,5-diCl	84.0	235	6.69-7.87	—	—	9.31	24
8	H	3,4-diCl	87.3	218	6.70-7.90	—	—	9.32	24
9	H	3-Cl, 4-OCH_3	87.0	215	6.85-7.85	3.84	—	8.61	8
10	H	3-Cl, 2-CH_3	89.5	240	6.85-7.75	—	2.25	8.69	70
11	H	3-Cl, 4-CH_3	90.0	230	6.86-7.78	—	2.25	8.70	4
12	H	4-NO_2	84.6	208	6.87-8.41	—	—	9.47	12
13	4-Cl	4-Cl	84.8	280	7.08-7.81	—	—	8.80	8
14	4-Cl	2-CF_3	86.2	227	7.24-8.14	—	—	9.47	8
15	4-Cl	3-CF_3	86.7	197	6.95-8.12	—	—	9.31	100
16	4-Cl	4-OPh	88.9	237	6.45-7.59	—	—	8.45	8
17	4-Cl	2,4-diCl	83.4	250	7.05-7.81	—	—	9.35	24
18	4-Cl	2,5-diCl	84.9	270	7.01-7.85	—	—	9.62	14
19	4-Cl	3,4-diCl	86.5	246	7.18-7.87	—	—	9.40	100
20	4-Cl	3-Cl, 4-OCH_3	85.5	220	7.03-7.77	3.84	—	8.71	20
21	4-Cl	3-Cl, 2-CH_3	87.4	270	7.07-7.94	—	2.25	8.74	10
22	4-Cl	3-Cl, 4-CH_3	85.2	252	7.10-7.89	—	2.25	8.70	18
23	4-Cl	4-NO_2	88.7	238	7.22-8.35	—	—	9.39	46

IR spectra of the compounds exhibited νC=O at 1640-1650 cm^{-1}

Among the twenty three diphenylureas synthesised and tested for IGR activity, two compounds **15** and **19** [1-(4-chlorophenyl)-3-(3-trifluoromethylphenyl)urea and 1-(4-chlorophenyl)-3-(3,4-dichlorophenyl)urea] exhibited promising IGR activity against *Cx. quinquefasciatus* larvae. These compounds may play a useful role in mosquito control by maintaining the vector populations at a minimum level with minimum deleterious effects on the environment by formulating these compounds in a suitable vehicle as a slow release formulation and applied in integrated vector management programmes.

Experimental Section

General. Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer-783 infrared spectrophotometer using KBr. ^{1}H NMR spectra were recorded on a Hitachi R-600 spectrometer using TMS as internal standard and $CDCl_3$ + DMSO-d_6 as solvent.

Preparation of compounds 1-23: General procedure. The acid chloride was prepared by refluxing the respective acid (0.15 mole) with slight excess of thionyl chloride (0.2 mole) for 1 hr over a steam-bath followed by removal of the excess thionyl chloride under reduced pressure, and purified by distillation.

Freshly distilled acid chloride (0.01 mole) in 20 mL of acetone taken in a separating funnel was added dropwise to a solution of sodium azide (0.9 g, 0.014 mole) in 5 mL of water taken in a two-necked R.B. flask. The experiment was carried out at 0-5 °C with magnetic stirring for 3 hr. The reaction mixture was extracted with 50 mL benzene, washed with water and finally dried over anhydrous $MgSO_4$.

The benzene solution of the acid azide taken in a 100 mL R.B. flask fitted with a gas trap was refluxed on a water-bath for 1-2 hr till the evolution of N_2 ceased. To the phenylisocyanate generated *in situ* was added the appropriate aniline

(0.01 mole) in benzene and the refluxing continued for 2-3 hr. The solvent was removed under reduced pressure and the diphenylurea obtained as a solid was recrystallized from ethyl alcohol. The percentage yield, melting points, ^{1}H NMR and IR spectral data of diphenylureas are given in Table I.

Evaluation of compounds for IGR activity against *Cx. quinquefasciatus*. The IGR activity of diphenylureas against III instar larvae of *Cx. quinquefasciatus* was determined using standard procedure[16,17]. One per cent solution of the test compound was made in acetone, from which 250 mg/L stock solution was prepared in acetone. One mL of the stock solution was added to 249 ml of tap water taken in a 500 mL beaker. Early III instar larvae of *Cx. quinquefasciatus* (25 in number) were exposed continuously to the test compound. A pinch of larval food (125mg) consisting of yeast powder and dog biscuit (1:1) was provided after 24 hr. Four replicates were set up for each concentration along with a simultaneous control with tap water containing 1 mL of acetone. Mortality of the larvae and pupae was recorded daily. The pupae were regularly collected and transferred to untreated water in 50 mL beakers. The experiment was conducted at 28±2 °C and 70-80% relative humidity. In recording the percentage effect, moribund and dead larvae and pupae as well as adult mosquitoes having not completely emerged from the pupal case and flown out, were considered as 'affected'.

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